Quality of life in primary aldosteronism: A prospective observational study

QUALITY OF LIFE IN PRIMARY ALDOSTERONISM: A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Background Previous studies suggested that patients affected by primary aldosteronism (PA) have impaired quality of life (QOL) compared to the general population, but a direct comparison with patients affected by essential hypertension (EH) has never been performed. The aim of the study was to compare the QOL of patients affected by PA to the QOL of patients affected by EH.

Material and methods

We designed a prospective observational study comparing the QOL of patients with PA and carefully matched patients with EH before and after treatment. We recruited 70 patients with PA and 70 patients with EH, matched for age, sex, blood pressure levels and intensity of anti-hypertensive treatment. We assessed QOL at baseline and after specific treatment for PA or after optimization of medical therapy for patients with EH.

Results

Patients with PA displayed impaired QOL compared with the general healthy population, but similar to patients with EH. Both laparoscopic adrenalectomy and treatment with mineralocorticoid receptor antagonist allowed an improvement of QOL in patients with PA, that was more pronounced after surgical treatment. Optimization of blood pressure control by implementation of antihypertensive treatment (without MR antagonists) allowed a minimal improvement in only one of eight domains in patients with EH.

Conclusions

Patients with PA have impaired QOL, which is likely caused by uncontrolled hypertension and the effects of intensive anti-hypertensive treatment. Surgical and medical treatment of PA

allows a significant improvement of QOL, by amelioration of blood pressure control and, after surgical treatment, by reduction of anti-hypertensive treatment.

Introduction

The World Health Organization considers quality of life (QOL) a key component of "health" status and recommends to consider the effects of medical treatments by assessing patients' well-being with health related QOL evaluation.[1] The QOL of patients with primary aldosteronism (PA) has been neglected until 2010, when a significant reduction of QOL in patients with aldosterone producing adenoma (APA), compared with the Australian general population, was reported for the first time.[2] In the following years, these findings were confirmed in larger cohorts of patients with unilateral PA,[3–6] and similar findings were obtained in patients with bilateral or idiopathic hyperaldosteronism (IHA).[4,7]

Beyond QOL, primary aldosteronism has been associated with anxiety, depressive disorders and somatization.[8–11] Recent findings suggested that aldosterone levels might correlate with depressive symptoms in women with PA[12] and, more broadly, previous studies indicated a correlation between serum aldosterone levels and the prevalence of depressive disorders in patients without PA.[13,14]

Well-being is an essential component of QOL and a previous study reported lower psychological well-being in patients with PA, compared with normotensive control.[9] A following study reported contrasting results, with no differences in well-being of patients with PA compared to Dutch normative data.[11] Several explanations may be offered for the conflicting results, including the use of different questionnaires, a predominantly male cohort and the lack of an appropriate control group in one study.

PA is the most common cause of endocrine hypertension and affects about 4-6% of patients with arterial hypertension in the general population.[15,16] Beyond the strict criteria for PA, recent studies identified an autonomous aldosterone secretion in up to 20% of individuals with hypertension and up to one fifth of patients with normotension.[17,18] Specific PA treatments, both unilateral adrenalectomy and medical treatment with mineralocorticoid receptor (MR)

antagonists, resulted in significant QOL improvement, that occurred earlier and was more pronounced in surgically treated patients compared with those medically treated.[4,7]

Some authors proposed that the impaired QOL of patients with PA could be attributed to the direct effects of aldosterone excess on central nervous system. However, uncontrolled and resistant hypertension could themselves account for a significant impairment of QOL.[19] No study directly compared the quality of life of patients with PA versus patients with essential hypertension with similar clinical characteristics. At the same time, in most of the former studies, QOL was assessed after PA diagnosis,[2,4] making the awareness of the disease a relevant component in QOL evaluation. Finally, no study compared the effect of specific treatment for PA versus optimization of medical treatment.

In this context, we designed a prospective observational study comparing, for the first time, the QOL of patients affected by PA (before diagnosis) with patients affected by essential hypertension (EH), matched for age, sex, blood pressure levels and intensity of drug treatment. We evaluated the modification of QOL after specific treatment in patients with PA and compared with QOL modification after optimization of anti-hypertensive therapy in the control cohort. In order to compare our study with previous findings[2-7], we adopted RAND SF-36 as tool to investigate QOL in our cohort.

Materials and methods

Study Design

The protocol was approved by the ethical committee of the hospital A.O.U. Città della Salute e della Scienza di Torino and written informed consent was obtained from all recruited patients. Reporting of the study conforms to broad EQUATOR guidelines.[20]

In the QUALIty of Life of patients with PA in TOrino (QUALITO) study we prospectively enrolled 140 patients (70 patients with PA and 70 matched controls with EH) from 03/2017 to 09/2019 in Torino, Italy. Patients with PA and EH were matched for sex, age, systolic blood

pressure (SBP) and intensity of antihypertensive drug treatment (quantified by daily defined dose, calculated with the online tool available at https://github.com/ABurrello/PASOPredictor/raw/master/00 - PASO Predictor.xlsm).[21]

All the included patients were affected by arterial hypertension, diagnosed according with the European Society of Cardiology/European Society of Hypertension (ESC/ESH) guideline [22,23]; diagnosis of EH was made after the exclusion of all the main secondary forms of arterial hypertension (including hypercortisolism, pheochromocytoma, hyperthyroidism and reno-vascular hypertension), while patients with PA were included following a confirmed diagnosis according to the Endocrine Society guideline and the recent ESH consensus.[24–26] The only exclusion criterion for EH cohort was treatment with MR antagonists at recruitment or at follow up. For PA cohort, exclusion criteria were I) patients under MR antagonist or II) previous adrenalectomy for unilateral PA at recruitment.

Diagnosis of primary aldosteronism

Before screening test, all interfering antihypertensive drugs were stopped (at least 2 weeks for ACE-I, ARBs and beta blockers and 4 weeks for diuretics). When complete discontinuation of antihypertensive treatment was not feasible, non-interfering drugs were administered. The screening test was considered positive in case of serum aldosterone ≥ 10 ng/dl and aldosterone to renin ratio (ARR) ≥ 30 ng/dl/ng/ml/h or aldosterone to active renin ratio (AARR) ≥ 2.7 ng/dl/mU/l. Seated saline infusion test (SSIT) or, in case of contraindication, captopril challenge test (CCT), were used as confirmatory tests. PA was considered confirmed in case of serum aldosterone post-SSIT ≥ 5 ng/dl or ARR ≥ 30 ng/dl/ng/ml/h after CCT.

Subtype diagnosis was performed by computed tomography of the adrenal glands and unstimulated and/or cosyntropin-stimulated adrenal venous sampling (AVS). A selectivity index ≥ 3 for unstimulated and ≥ 5 for stimulated AVS was used to define successful

cannulation of adrenal veins. A lateralization index ≥ 4 or ≥ 3 with contralateral suppression (contralateral ratio < 1) was used to define unilateral PA.

Quality of life data collection

36-Item Short Form Health Survey (RAND SF-36) is a self-administered questionnaire used to assess health-related QOL and validated in the Italian population.[27] RAND SF-36 includes 35 items and 8 different subscales: physical functioning, role limitations due to physical problems, role limitations due to emotional problems, vitality, general mental health, social functioning, bodily pain, and general health perceptions.

At baseline, RAND SF-36 was self-administered in patients with PA before confirmatory test and in patients with EH before optimization of antihypertensive medical treatment.

In the PA cohort, RAND SF-36 was also collected 2 and 6 months after laparoscopic surgical adrenalectomy or initiation of MR antagonist. RAND SF-36 was collected 6 months after optimization of medical treatment in patients with EH.

Data of the PA cohort, at baseline and at 6 months, have been compared to the Italian normative data from "healthy subjects".[27]

Statistical methods

IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, New York) was used for statistical analyses. PRISM software (GraphPad, San Diego, CA) was used for charts and graphs preparation. Data are expressed as mean ± SD for continuous variables with a normal distribution. Data with non-normal distributions are expressed as median (interquartile range). Charlson Comorbidy index was used to estimate burden of comorbidity and considered as categorical variable.[28] Statistical significance between groups was calculated in normally distributed data by paired t test for groups of matched patients and Student t test for independent samples in other cases. Mann-Whitney U test was used for non-normally distributed data and Kruskal-Wallis test for paired samples for non-normally distributed data of matched samples.

Chi-square test was used for qualitative variables. Repeated measure ANOVA was used for comparison of daily defined dose (DDD) and blood pressure levels during follow up.

Linear mixed model is a statistical approach that can be applied in prospective studies for the analysis of repeated measures. In contrast to repeated measure ANOVA, usually used for repeated measures analysis, mixed models consider both fixed and random effects, allowing a more accurate analysis of prospective data. Moreover, using random effects for baseline values, mixed models take into account differences in starting point for each subject.

Linear mixed models, with unstructured correlation and maximum likelihood method, were used for longitudinal comparison of QOL changes and performed with R version 3.6.1. Scores of the 8 subscales of RAND SF-36 were used as dependent variables. Time, treatment, sex, diabetes and CCI were considered as fixed factors and potassium, creatinine, age, BMI and duration of hypertension as covariates. 20 different models were evaluated for each subscale and minimum Akaike information criterion (AIC) was used for model selection (Supplemental Methods).

Results

PA and EH cohort

A total of 140 patients were recruited for the QUALITO study in Torino: 70 patients with PA and 70 patients with EH matched for age, sex, systolic blood pressure and intensity of anti-hypertensive drug treatment (DDD). Of the 70 patients with PA, 43 were diagnosed as affected by unilateral PA, 37 of whom underwent laparoscopic adrenalectomy (Figure S1). All the patients that underwent unilateral adrenalectomy displayed complete biochemical outcome at 6 months follow-up according to PASO criteria.[29] Twenty out of 70 patients with PA were classified as IHA and 7 patients with undetermined subtype, because unwilling to undergo AVS or unsuccessful procedure. Thirty patients were treated with MR antagonist (14 with spironolactone, 16 with potassium canrenoate), including 6 patients with unilateral PA, 19

patients with IHA and 5 with undetermined subtype. One of 37 patients after surgical adrenalectomy and one of 30 patients under MR antagonist were lost at follow up (Figure S1). Principal clinical and biochemical characteristics of patients with EH and PA are summarized in Table 1. No significant differences were present between the two cohorts for the evaluated parameters, except for lower serum potassium in PA cohort.

Baseline comparison

At baseline, patients with PA had non-significant differences in either of the 8 subscales compared with matched individuals with EH (Figure 1, Table S1). No differences were present even after stratification for subtype diagnosis, in patients with unilateral PA and IHA (Table S2-S3), compared with the respective matched patients with EH.

Compared to Italian normative data of "healthy subjects",[27] patients with PA displayed lower score in 5 of 8 domains: physical functioning, role limitations due to physical health problems, vitality, social functioning and general health perceptions (Figure 1, Table S1), with similar results in patients with unilateral PA and IHA, with the exception of social functioning, that did not differ significantly between patients affected by IHA and healthy subjects (Table S2-S3). At baseline, independently of PA or EH diagnosis, patients with DDD≥3 displayed lower QOL in two physical subscales than patients with DDD<3 (Tables S4).

Follow up

After surgical adrenalectomy, patient with APA displayed a significant reduction, at 2 and 6 months of follow up, of SBP (149±13 *vs* 124±11 *vs* 121±11 mmHg), diastolic blood pressure (DBP) (92±9 *vs* 80±11 *vs* 78±8 mmHg) and anti-hypertensive treatment (DDD 3.05±1.68 *vs* 1.31±1.53 *vs* 0.94±1.26). Patients under MR antagonist showed a reduction of SBP (145±15 *vs* 134±14 *vs* 131±13 mmHg) and DBP (88±9 *vs* 83±9 *vs* 83±8 mmHg) with a non-significant increase of anti-hypertensive treatment (DDD 3.07±1.24 *vs* 3.43±1.42 *vs* 3.44±1.44).

Similarly, patients treated with general anti-hypertensive treatment showed SBP and DBP reduction at 6 months, with increased DDD (Table S5).

We used linear mixed models to compare baseline values with follow up scores at 2 and 6 months after treatment, selecting the best of 20 tested models, for each of the 8 subscales (Supplemental Methods and Table S6). Effect and statistical significance of fixed factors, covariates and interactions in each of the 8 subscales are showed in Table S7.

During follow up, patients undergoing unilateral surgical adrenalectomy displayed a significant improvement in 4 of 8 domains: physical functioning, vitality, general health perceptions and general mental health, with the latter significant at 2 but not at 6 months. Patients with PA treated with MR antagonist, had a significant improvement in 2 domains: physical functioning and general health perceptions. Patients with EH undergoing optimization of anti-hypertensive treatment without MR antagonist displayed a significant improvement in only one domain (general mental health) at 6 months of follow up (Figure 2A-B-C, Table S8).

Six months comparison

At 6 months, adrenalectomized patients displayed higher scores in physical activity and general health perceptions, compared to patients under general anti-hypertensive treatment, and higher score in social functioning, compared to patients under MR antagonist. Patients with PA under MR antagonist had higher score of physical functioning compared to patients under general anti-hypertensive treatment (Figure 2D, Table S9).

Six months after surgery, adrenalectomized patients displayed similar score in 7 of 8 domains, compared to Italian normative data of healthy subjects,[27] with lower score in only general health perception. Instead, after 6 months of medical treatment, patients with MR antagonist had lower scores in 4 of 8 domains compared to healthy subjects (Figure 3, Table S10).

Discussion

QOL is a well-recognized component of health and QOL assessment has an important role in the evaluation of the impact of diseases on affected patients. Whether the impaired QOL of patients affected by PA is the result of aldosterone effect on the central nervous system or the consequence of uncontrolled blood pressure is still an open question.[30]

In the QUALITO study we compared, for the first time, the QOL of patients affected by PA to the QOL of carefully matched patients affected by EH, as control group. The scores of patients affected by PA were lower than healthy subjects, but not different from those of patients affected by EH, suggesting that the impairment of QOL in PA could be attributable to uncontrolled blood pressure and anti-hypertensive treatment, more than a direct effect of aldosterone excess.

Female sex, obesity and metabolic syndrome have been related to reduced QOL in previous studies.[3,31] Supporting these findings, in our study, sex female had a significant negative impact on 6 of 8 domains, including both physical and emotional subscales; similarly, high BMI had a significant negative impact in role limitations due to physical health problems and general health perception. Considering the known relationship between primary aldosteronism, obesity and metabolic syndrome, it is possible that the coexistence of these conditions may synergistically contribute to the reduction of QOL in patients with PA.[32]

In agreement with previous studies,[2–4,7] we observed that both surgical and medical treatments for PA induced a significant improvement in QOL, that was remarkably more pronounced in the surgery group compared with the MR antagonist group. The optimization of anti-hypertensive treatment, without MR blockade, in patients affected by EH, resulted into a minimal increase in only one of 8 domains of QOL. This result suggests that reduction of blood pressure levels *per se*, is probably not sufficient for a significant improvement of QOL and that a specific role for MR antagonists, beyond its anti-mineralocorticoid activity, can be hypothesized.

Multiple factors are likely working synergistically, reducing QOL in patients with hypertension and PA, including disease awareness, medical treatment and uncontrolled blood pressure. Knowledge of the disease is a key component of impaired QOL in many conditions. Patients aware of the diagnosis of arterial hypertension have lower QOL than patients unaware of the disease, independently of blood pressure levels.[33] Therefore, patients' perception of PA-related cardiovascular risk, the need of invasive procedure for subtype diagnosis (such as adrenal venous sampling) and lifestyle recommendations (such as dietary modification) can further impact their QOL. In our study, the questionnaire was administered before PA diagnosis, thus eliminating the potential bias of disease-awareness.

Another important factor affecting the QOL is represented by anti-hypertensive treatment. In a previous study, the QOL in physical and mental components was higher in patients taking < 4 anti-hypertensive medications than in patients taking a higher number of drugs. The association between number of drugs and mental component was significant even after correction for the main confounding factors including blood pressure levels.[34] We confirmed this finding, reporting lower QOL in patients with DDD≥3 than patients with DDD<3 at baseline evaluation, independently from the final diagnosis (PA or EH).

In our study, patients treated with MR antagonist or optimization of anti-hypertensive treatment achieved blood pressure control by increase of drug treatment. On the counterpart, six months after surgery, the mean DDD dropped to less than 1 in patients adrenalectomized. This difference probably contributes to the significant improvement in QOL observed in patients undergoing surgical treatment for unilateral PA, allowing a normalization of QOL scores in 7 of 8 domains, compared to healthy subjects.

Among patients with hypertension under anti-hypertensive treatment, the highest QOL in physical component is encountered in those with SBP around 125 mmHg and DBP around 75 mmHg.[34] After surgery, adrenalectomized patients displayed lower blood pressure levels than

patients under MR antagonist or general anti-hypertensive treatment, with values close to the figures reported above. Therefore, beyond reduction of anti-hypertensive treatment, the achievement of lowest blood pressure could probably contribute to the better quality of life in adrenalectomized patients.

The importance of psychosocial stress in arterial hypertension has been largely evaluated in the last decade. A recent study expanded this concept, introducing and highlighting the importance of allostatic load in arterial hypertension.[35] Allostatic load is the reflection of cumulative effects of daily life experiences, including ordinary and extra-ordinary events.[36] Allostatic load is significantly more prevalent in patients with arterial hypertension than individuals with normotension and patients with hypertension and allostatic load display significantly decreased quality of life.[35] The role of allostatic load in PA has never been evaluated. This aspect should probably be investigated in future studies to better elucidate the development of impaired QOL in PA.

Patients with PA treated with MR antagonist displayed a significant increase in the score related to physical functioning and general health perceptions. In particular, the physical functioning score was significantly higher after 6 months, compared to patients with EH treated with medical treatment, without MR blockade. This finding may suggest a direct role of MR antagonist in the improvement of physical functioning, beyond blood pressure control *per se*. High aldosterone levels have been associated with significantly lower exercise capacity in patients with chronic heart failure,[37] and spironolactone significantly improved exercise tolerance.[38] Spironolactone may act by reduction of myocyte apoptosis and enhancing of skeletal muscle contractility.[39]

The limits of our study are the absence of a control group of patients with PA treated with optimization of medical treatment without MR blockade, the absence of a control group of patients with EH treated with MR antagonist, the absence of a control group of normotensive

subjects collected in the same setting and the lack of anxiety and depression symptoms evaluation. The strengths and novelties of this study are the comparison of QOL of patients with PA with matched patients with EH, the comparison of specific treatments for PA (adrenalectomy and MR antagonist) *versus* optimization of medical treatment in a similar group of patients, the diagnosis and subtype diagnosis of PA according to guidelines, and the administration of the first questionnaire for QOL assessment before PA diagnosis.

In conclusion, patients with PA displayed lower QOL than healthy subjects, but not different from matched patients with EH. Treating patients affected by APA with surgical adrenalectomy allows a better control of blood pressure levels, with lower anti-hypertensive treatments, reaching a significantly higher QOL at medium term follow up than medical therapy alone. Treatment with MR antagonist allows a significant improvement in physical aspects of QOL compared to optimization of medical therapy without MR blockade.

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Author contributions: F.B., G.C., S.M. and P.M. designed the study; F.B., G.C., E.S., A.P. and M.T. collected data; F.B., M.A., J.B. analyzed data; S.M., P.M. and F.V. supervised the entire study; F.B., G.C., S.M., P.M. wrote the original draft; all authors reviewed and edited the final manuscript.

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Figure Legends

Figure 1. Baseline QOL: PA vs. EH-matched controls and healthy subjects. Comparisons were performed by paired t-test for PA vs. EH and unpaired t-test for PA vs. healthy subjects. QOL=quality of life, PA=primary aldosteronism, EH=essential hypertension, PF=physical functioning, RLP=role limitations due to physical problems, RLE=role limitations due to

emotional problems, V=vitality, GMH=general mental health, SF=social functioning, BP=bodily pain, GHP=general health perceptions. * = significant at p<0.05 PA vs. healthy subjects.

Figure 2. Longitudinal comparison of QOL and cross-sectional comparison at 6 months in patients with different treatments. Comparisons are considered significant at at p<0.05. Figure 2A-2B-2C: * = 6 months vs. Time 0, † = 2 months vs. Time 0. Figure 2D: * = adrenalectomy vs. general anti-HT treatment, † = MR antagonist vs. general anti-HT treatment, ‡ = adrenalectomy vs. MR antagonist. Estimated mean scores comparison have been performed by linear mixed models (details in Supplemental Methods).

PF=physical functioning, RLP=role limitations due to physical problems, RLE=role limitations due to emotional problems, V=vitality, GMH=general mental health, SF=social functioning, BP=bodily pain, GHP=general health perceptions, MR=mineralocorticoid receptor, anti-HT=anti-hypertensive.

Figure 3. Six months QOL: patients treated with ADX and MRA vs. healthy subjects. * = significant at p<0.05 adrenalectomy vs. healthy subjects, † = MR antagonist vs. healthy subjects. Comparisons were performed by unpaired t-test.

PF=physical functioning, RLP=role limitations due to physical problems, RLE=role limitations due to emotional problems, V=vitality, GMH=general mental health, SF=social functioning, BP=bodily pain, GHP=general health perceptions, MR=mineralocorticoid receptor.

Table 1. Descriptive Statistics

	PA (n = 70)	**EH (n=70)**	**p-value**
Age (years)	52±9	54±10	0.199
Sex Male Female	 45 (64.3) 25 (35.7)	 45 (64.3) 25 (35.7)	1.000
SBP (mmHg)	146±14	143±13	0.118
DBP (mmHg)	90±10	90±9	0.806
DDD	3.02±1.46	2.83±1.35	0.427
Duration of hypertension (years)	5 (1-10)	7 (1-16)	0.233
Creatinine (mg/dl)	0.87±0.21	0.91±0.19	0.385
Sodium (mmol/l)	141±2	142±2	0.103
Potassium (mmol/l)	3.6±0.5	4.1±0.4	<0.001
BMI (kg/m^2)	25.9±4.1	26.9±5.4	0.196
Type 2 diabetes mellitus No IFG Diabetes	 67 (95.7) 3 (4.3) -	 66 (94.3) 4 (5.7) -	0.698
Presence of comorbidity by CCI	9 (12.8)	20 (28.6)	0.152

PA=primary aldosteronism, EH=essential hypertension, SBP=systolic blood pressure, DBP=diastolic blood pressure, DDD=daily defined dose, BMI=body mass index, IFG=impaired fasting glucose, CCI=Charlson Comorbidity Index. Comparisons were performed by unpaired *t*-test for continuous variables and $\chi 2$ test for categorical variables.

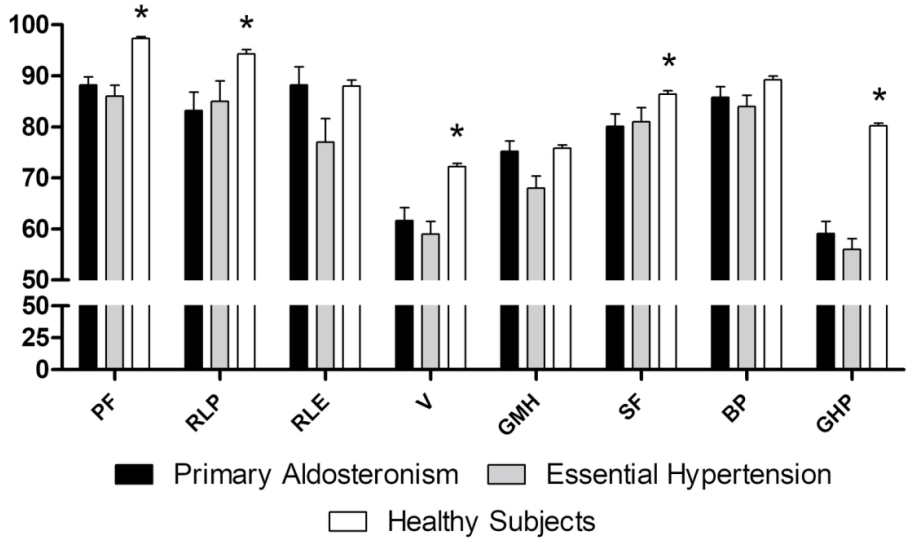

Figure 1. Baseline QOL: PA vs. EH-matched controls and healthy subjects.

137x86mm (300 x 300 DPI)

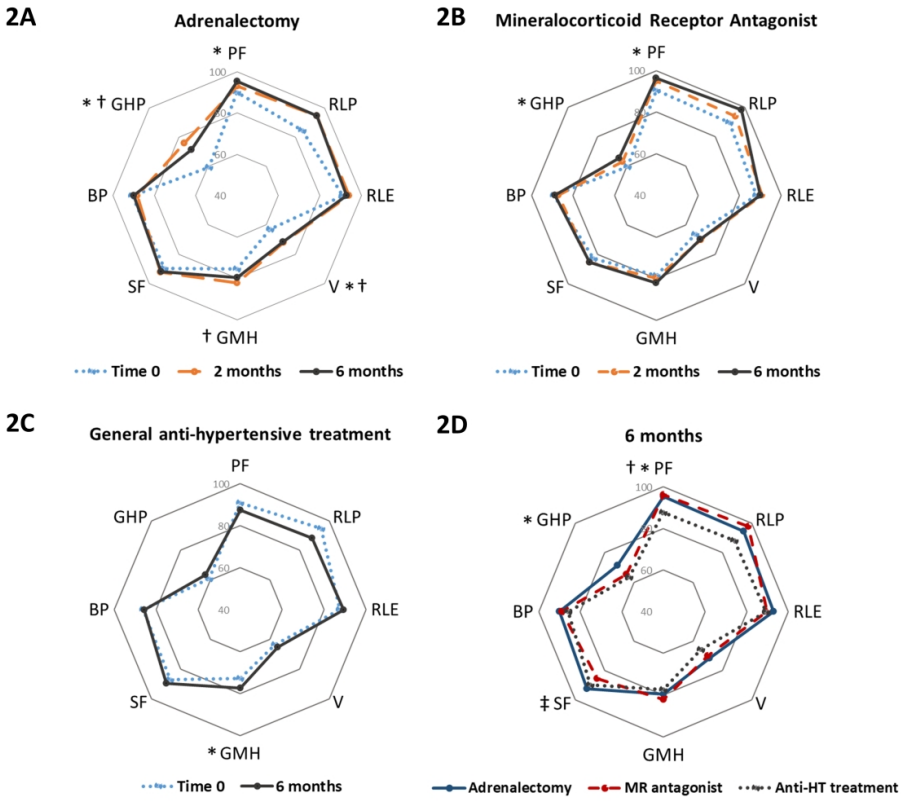

Figure 2. Longitudinal comparison of QOL and cross-sectional comparison at 6 months in patients with different treatments.

329x299mm (300 x 300 DPI)